PATENT
2801-0155p

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Susan M. DALUGE et al

Appl. No.: 08/957,045 Group: 1624

Filed: October 24, 1997 Examiner: M. Berch

For: CHLOROPYRIMIDINE INTERMEDIATES

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner for Patents
Washington, DC 20231

April 23, 2001

Sir:

I, Dr. Susan M. Daluge, hereby declare as follows:

I am an inventor of the above-identified application Serial No. 08/957,045 filed October 24, 1997.

I received a Ph.D degree in Organic Chemistry from the University of Minnesota Chemistry Department in 1969. I am a Principal Scientist in the Department of Medicinal Chemistry at Glaxo Wellcome, Inc.

I have studied the specification and I am familiar with this field of technology. I have received an American Chemical Society award for this chemistry.

I am intimately aware of the process disclosed in Daluge '697 (U.S. Patent 5,087,697), because I am also an inventor of Daluge '697. The Examiner has used Daluge '697 as the primary reference in the outstanding Office Action in a 35 U.S.C. §103(a) rejection. I now remark on the Examiner's rejection of the claims as being obvious over the cited prior art.

Protecting Group R^3 on Compounds of Examples 25-27 in Daluge '697

The present inventive process has significant advantages over the process of Daluge '697. Moreover, the Daluge '697 process has clear disadvantages. A synthetic scheme depicting Route 1 and Route 2 of Daluge '697 and the present invention is attached to this Declaration. Daluge '697 discloses a "research route", which is useful only to synthesize a few grams of the material; thus, the process is not useful for manufacturing of a drug, because of the complex mixtures formed. Examples 25-28 and Examples 3-4 are prepared only on a gram scale.

Chlorination of di-oxopyrimidine without blocking the amino groups with acyl groups results in tars and low yields. A tar coats the reactor, which means the process step cannot be scaled up. A tedious chromatography step is required for purification to get a low yield. To avoid these problems, Daluge '697 Route 1 blocks the amino group at the 2-position with isobutyric acid to make the purine.

The compound of Example 27 has a protecting group on the 2-amino position of the purine. The 6-chloropurine intermediate was not isolated in Example 27 because treatment with aqueous acid to remove the isobutryl group from the 2-position causes hydrolysis of the 6-chloro group to 6-oxopurine, lowering the yield. Instead, the crude mixture containing 6-chloropurines was subjected to reaction with cyclopropylamine and the resulting mixture (glass which could not be solidified) was then

chromatographed in order to isolate 53% of the desired 6-cyclopropylaminopurine on a gram scale after a difficult separation (large volumes of solvent, many fractions, and a high ratio of silica gel to compound required) from the compound in which the isobutryl group had been removed (partial removal during cyclopropanation). Example 28 is the deprotection step of the title compound of Example 27. The final product in Example 28 after another chromatography purification necessitated by the noncrystalline nature of the product (i.e. could not be solidified to purify) results in an 80% yield.

Examples 3 and 4 in Daluge '697

The compound in Example 3 of Daluge '697 is a triaminopyrimidine, which is not suitable for a large-scale process. The compound is air sensitive, light sensitive, heat sensitive, and chelates metals (undesirable, potentially toxic impurities in final drug resulting). The compound is a dark oil that could not be solidified to effect purification. Extensive chromatography was necessary to obtain a solid with sufficient purity to enable use as an intermediate for synthesis of final cyclopropylaminopurine. Once purified, the compound must be stored in a dark cold inert atmosphere, which is a problem in a scale-up process plant.

Example 4 in Daluge '697 describes a very difficult reaction with following work-up. Example 4 uses diethoxymethyl acetate instead of trialkylorthoformate. The complex mixture of products

from the procedure disclosed in Example 4 was purified by chromatography to produce a 46% yield of the final product on a gram scale.

Summary of the Process of the Present Invention versus the Process of Daluge '697

The process of the present invention uses a trialkylorthoformate in the presence of aqueous acid to cause ring formation of the purine. A protection group is not needed on the 2-position amine to give good yield. This was unexpected.

The attached synthetic route of the present invention shows Compounds of formula III, which are achieved in high yield and purity. The previous synthetic step uses transient blocking during chlorination to avoid the tars; thus, the compounds are purified by simple precipitation. This reaction is done on thousands of kilogram scale. Compounds of formula (III) are more reactive to amines; thus, a shorter reaction time is needed.

Compounds of formula VI are much improved over the compound of Example 3, because they are not air sensitive, light sensitive or heat sensitive. They are solids purified by precipitation. It is such a clean reaction typically the compound does not require purification. Compounds of formula VI do not chelate metals and are stable indefinitely at room temperature.

Compounds of formula VII are formed cleanly from compounds of formula VI and are isolated by precipitation. An unexpected part of the synthesis is that the CHO of formula VI is removed

during the formation of formula VII. This was discovered by ^{13}C-label of the formyl group in formula VI.

Conclusion

A significant difference exists between the process of the present invention and the process as described in Daluge '697. In Daluge '697 and the other cited prior art the reaction steps lead to impurities and difficult purification steps. Therefore, the synthetic routes described in Daluge '697 produce the compounds in Example 4 and 28 at lower yields and purity; thus, these process steps are not useful in a large scale manufacturing process. The process of the present invention is unexpectedly superior to the processes of Daluge '697.

The CHO group in the compounds of formula (III) provides for the improved physical properties of the compounds of formula (VI). Therefore, the final products of formula (VII) are clean and suitable for drug synthesis.

The above statements show that side-reactions persist in the process of Daluge '697 without protecting groups and the present process unexpectedly has superior results without the need for a deprotection step near the end of the total synthetic pathway.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

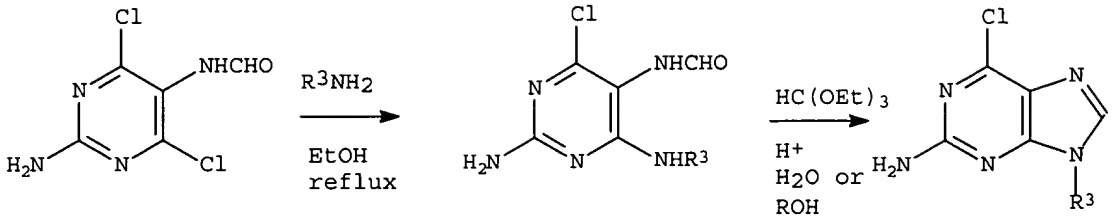
under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 27, 2001
Date

By: Susan M. Daluge
Dr. Susan M. Daluge

Attachment to 37 C.F.R. §1.132 Declaration

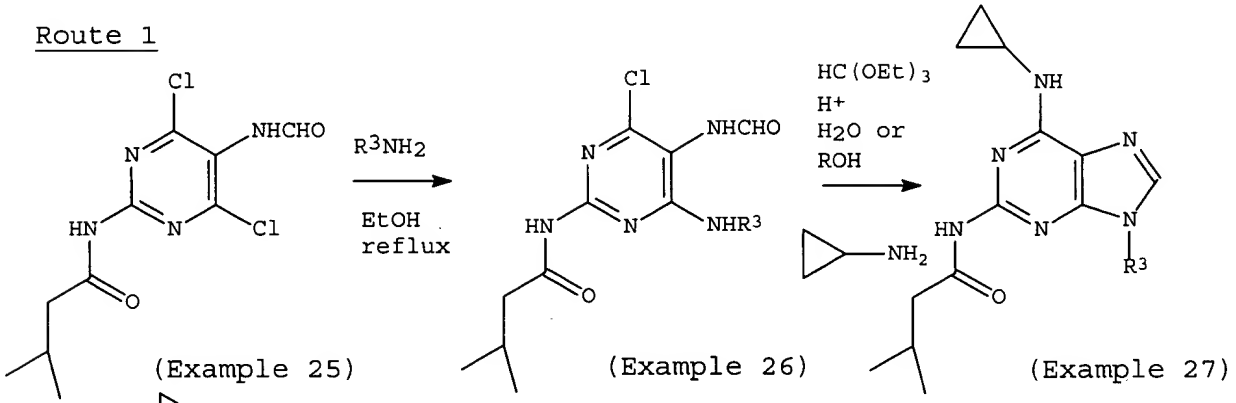
Present Inventive Process



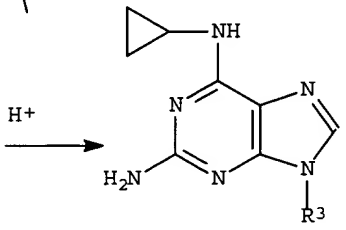
(III) (VI) (VII)

Daluge '697 Processes

Route 1

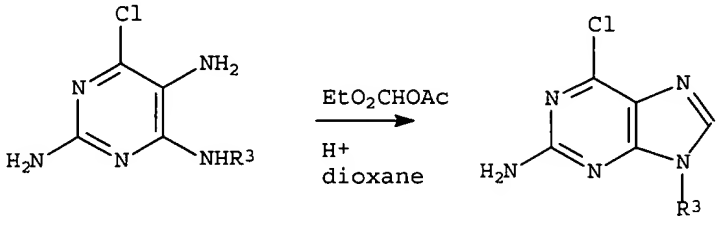


(Example 25) (Example 26) (Example 27)



(Example 28)

Route 2



(Example 3) (Example 4)